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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF APPEALS AND INTERFERENCES

Application of: Burchard

Serial No.: 09/616,849

Filed: July 14, 2000

For: METHOD FOR DETERMINING THE SPECIFICITY AND SENSITIVITY OF OLIGONUCLEOTIDES FOR HYBRIDIZATION

Confirmation No.: 6450

Art Unit: 1634

Examiner: Forman, B. J.

Attorney Docket No: 9301-044

REPLY BRIEF

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REPLY BRIEF UNDER 37 C.F.R. § 41.41

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Sir:

In response to the Examiner's Answer (hereinafter the "Answer"), mailed January 31, 2007, and in accordance with 37 C.F.R. § 41.41, Appellant respectfully submits this Reply Brief and requests consideration of the remarks made herein. Appellant's Brief on Appeal was filed on November 7, 2006 (hereinafter the "Appeal"). Since March 31, 2007 is a Saturday, the Reply Brief is hereby timely filed on April 2, 2007.

It is estimated that no fee is required for filing this Reply Brief. However, should the Patent and Trademark Office determine otherwise, please charge the necessary fee to Jones Day Deposit Account No. 50-3013.

REPLY TO THE EXAMINER'S ANSWER

Appellant respectfully maintains the arguments as set forth in the Brief on Appeal (hereinafter the "Appeal"), which was filed on November 7, 2006 and which is hereby incorporated by reference in its entirety. Furthermore, Appellant respectfully submits the following arguments in response to the Examiner's Answer (hereinafter the "Answer").

I. The Examiner's Response to Appellant's Arguments B1-B7 Relating to Claims 27, 29, 30, 33-40, 42-54, 59-60, 64-65, 67, 73 and 90-104 Is Erroneous

With respect to claims 27, 29-30, 33-40, 42-54, 59-67, 73-75, 84-85 and 90-104 being rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 4,900,659 ("Lo") in view of Lockhart *et al.*, Nature Biotechnology 14:1675-1680, hereinafter "the Lockhart Article"), Appellant respectfully submits that the responses in the Examiner's Answer to Appellant's arguments B1-B7, as set forth in the Appeal, are erroneous.

Teaching of Lo

Lo teaches a method for identifying, among different probes having unknown sequences, those that exhibit specificity to *N. gonorrhoeae* but not to *N. meningitidis*, wherein the genomic sequences of neither strain are taught by Lo. The probes of Lo are fragments from *N. gonorrhoeae* chromosomal DNA. In Lo, *N. gonorrhoeae* chromosomal DNA is digested into fragments (see Lo at column 5, lines 16-68). Each of the fragments is inserted into a vector to form a recombinant molecule (see Lo at column 6, lines 6-51). The recombinant molecule is transformed into a suitable host, e.g., *E. coli* (see Lo at column 6, line 52 through column 7, line 57). The recombinant molecules are amplified (Lo, col. 7, Section E). The recombinant molecules are then screened against *N. gonorrhoeae* and *N. meningitidis* chromosomal DNAs to identify those sequences that are specific for *N. gonorrhoeae* (Lo, col. 8, Section F). The screening is carried out using test dots each consisting of denatured purified chromosomal DNA from either *N. gonorrhoeae* or *N. meningitidis*, i.e., each test dot consists of chromosomal DNA from one strain of *N. gonorrhoeae* or *N. meningitidis* (see Lo at column 8, lines 13-19). Lo does not teach preserving the integrity of chromosomal DNA extracted from the bacteria. Instead, Lo teaches shearing the DNA molecules by passing the molecules through a syringe needle (see Lo at column 22, lines 11-15). Thus, Lo's test dot contains randomly generated

fragments of a strain of *N. gonorrhoeae* or *N. meningitidis*. A recombinant molecule is identified if the ratio of its hybridization amount to a test dot containing fragments of chromosomal DNA of a strain of *N. gonorrhoeae* and its hybridization amount to a test dot containing fragments of chromosomal DNA of a strain of *N. meningitidis* is greater than a preset value, *e.g.*, five (see Lo at column 10, lines 55-67). Thus, Lo teaches a method of identifying probes that exhibit a ratio of hybridization to a test dot containing fragments of chromosomal DNA of a strain of *N. gonorrhoeae* and hybridization to a test dot containing fragments of chromosomal DNA of a strain of *N. meningitidis* where the sequences of the probes are not known.

Teaching of the Lockhart Article

The Lockhart Article teaches methods for expression monitoring using pairs of perfect match and mismatch probes on a high density DNA microarray (the Lockhart Article, at page 1676, right column, third paragraph). In the Lockhart Article, a method is disclosed for selecting probes based on the sequence features of the probes. The method involves hybridizing respectively pools of specific cytokine RNAs and complex RNA populations that do not contain the cytokine RNAs to the 16,000 probe murine cytokine arrays (of more than 16,000 probes) (the Lockhart Article, at page 1680, left column, third paragraph). Data obtained from these experiments were used to extract a set of heuristic rules by a direct analysis of probe behavior as a function of certain sequence features or to train a neural network model (the Lockhart Article, page 1680, left column, third paragraph). The 16,000 probe arrays contain for each target RNA a set of probe pairs, each probe pair containing a perfect-match probe (PM) and a mismatch probe (MM) (the Lockhart Article, page 1676, right column, second and third paragraphs). The abundance of a target RNA is determined based on the difference between the signals of a PM probe and a corresponding MM probe (see the Lockhart Article at page 1679, right column). Thus, the Lockhart Article teaches selection of probes according to the difference in binding properties of a PM and a MM, not according to a ratio between the amount of a probe's hybridization to the pool of specific cytokine RNAs and the amount of probe's hybridization to the complex RNA population that did not contain the cytokine RNAs.

In the following, Appellant respectfully submits replies to the Examiner's Answer to Appellant's arguments B1-B7, in the same order as set forth in the Appeal.

The Examiner's Response to Appellant's Argument B1 Relating to Claims 27, 29, 30, 33-40, 42-54, 59-60, 64-65, 67, 73 and 90-104 Is Erroneous

Motivation to Combine

In response to Appellant's argument B1 relating to claims 27, 29, 30, 33-40, 42-54, 59-60, 64-65, 67, 73 and 90-104, the Examiner once again contends that the Lockhart Article "provide[s] clear motivation for evaluating probes using probes having predetermined base sequence i.e. the method of probe selection, based on sequence information" (see Answer at page 13, last paragraph, bridging to page 14, first paragraph). The Examiner does not provide any analysis or present any evidence to support such contention. Instead, the Examiner merely quotes a sentence from the abstract of the Lockhart Article: "[the method in the Lockhart Article] 'provides a way to use directly the growing body of sequence information for highly parallel experimental investigation.... simultaneous monitoring of tens of thousands of genes' (Abstract)" (see, Answer, at page 14, first paragraph, bridging from page 13). The Examiner further dismisses Appellant's previous argument that one would not be motivated to alter the method of Lo because Lo uses randomly generated fragments by repeating that the Lockhart Article provides the clear motivation without providing any further alleged evidence thereof. Similarly, on page 16, first paragraph of the Answer, the Examiner addresses Appellant's contention that the Examiner has not come forward with adequate motivation to combine the cited references, e.g., since there is no evidence of how sequence information may benefit Lo's method, by merely reiterating in a conclusory fashion, that "Lockhart clearly provides motivation for using probes of known sequence (see Abstract)."

Appellant respectfully points out that the relevant issue is whether the Lockhart Article provides one of ordinary skill in the art with motivation for using probes of known sequence in the method of Lo. The Examiner has come forward with no reason for why one would be so motivated.

Appellant respectfully maintains that the Examiner has not satisfied the burden of proof that the Lockhart Article provides clear motivation for one skilled in the art to combine the teaching of Lo with that of the Lockhart Article. Analysis based on established case law has been submitted by Appellant in the Appeal, from page 16, third paragraph, through page 20, first paragraph. The Examiner appears to be contending that motivation to combine the probes of known sequence of the Lockhart Article with the method of Lo, is found in the Lockhart Article abstract's alleged disclosure that probe selection based on

sequence information is useful for "highly parallel experimental investigations" involving the "simultaneous monitoring of tens of thousands of genes." However, expression analysis involving large scale monitoring of large number of genes, which is what the Lockhart Article is concerned with, is totally irrelevant to the purpose and concerns of Lo. Lo has nothing to do with such expression analysis. Instead, Lo is concerned with developing a probe that specifically detects *Neisseria gonorrhoeae* chromosomal DNA, in order to be able to diagnose infection by *Neisseria gonorrhoeae* (see Lo at columns 1-3 and column 16, lines 52-57). Lo has absolutely no interest in large scale expression analysis, and thus the Examiner's alleged motivation for the combination does not apply.

The Lockhart Article does not provide the clear motivation for one skilled in the art to combine the teaching of the Lockhart Article with Lo, because 1) Lo's invention does not need the teaching of the Lockhart Article, and 2) combining the teaching of the Lockhart Article with Lo adds little or no value to Lo or renders the invention of Lo useless, and destroys a disclosed advantage of Lo.

Lo's invention does not need the teaching of the Lockhart Article relating to use of probes of known sequence. The Lockhart Article teaches probe design based on known sequence information. Lo provides a method of identifying nucleic acid probes containing discrete nucleotide sequences that are specific for *Neisseria gonorrhoeae*, in that they do not significantly hybridize to the chromosomal DNA of the closely related *Neisseria meningitidis* (see, for example, Lo, column 10, lines 35-67). The identifying method in Lo uses probes, and test dots that are randomly generated by restriction enzyme digestion or shearing/sonication of the *Neisseria gonorrhoeae* chromosomal DNA (see, for example, Lo, column 5, lines 47-68, and column 15, lines 41-48). The source, but not the sequences, of the nucleic acid molecules in the probes and the test dots are known: a probe contains a nucleotide fragment from *Neisseria gonorrhoeae*, and a test dot contains nucleotide fragment from a strain of *Neisseria gonorrhoeae* or *Neisseria meningitidis*, but not both. The sequences of the probes and of the fragments composing the test dots are unknown and do not need to be known. Lo specifically points out the laborious nature of the sequencing process in an effort to distinguish their invention, thereby highlighting the advantage of the Lo invention that arises from the avoidance of using sequence information:

> It should be noted that the genome of any strain of *Neisseria gonorrhoeae* and *Neisseria meningitidis* is each about 3 million nucleotides. A skilled scientist can sequence about 2,000 nucleotides per month. Thus, it would take 3,000 scientists one month to sequence the genome of one strain of

Neisseria gonorrhoeae and one strain of *Neisseria meningitidis*.

See Lo at column 3, lines 40-46. Lo's invention is presented as an alternative to the laborious and time-consuming processes that require sequence information of either probes or test dot nucleic acids. In Lo, the probes are recombinant DNA molecules that contain DNA fragments randomly derived from only *N. gonorrhoeae* DNA (see, for example, Lo at column 5, line 16, through column 6, line 51). Lo teaches that the probes are labeled with the radioactive isotope ^{32}P (see, for example, Lo column 9 line 67 to column 10 line 2). Each of the test dots contains chromosomal DNA fragments randomly derived from a *N. gonorrhoeae* strain ***or*** a *N. meningitidis* strain (hereinafter referred to as a *N. gonorrhoeae* test dot or a *N. meningitidis* test dot, respectively). DNA fragments in the test dots are not labeled. A probe is hybridized separately to the *N. gonorrhoeae* test dots ***and*** to the *N. meningitidis* test dots. For each hybridization experiment, the amount of the probe that is bound to the *N. gonorrhoeae* test dots is obtained by quantifying the amount of radioactivity that is bound to the *N. gonorrhoeae* test dots; and the amount of the probe that is bound to the *N. meningitidis* test dots is obtained by quantifying the amount of radioactivity that is bound to the *N. meningitidis* test dots (see Lo at column 10, lines 8-50). After subtracting background, normalizing, and averaging, the results are compared to compute a binding ratio of *N. gonorrhoeae*: *N. meningitidis* (see Lo at column 11, line 13, though column 12, line 45). The binding ratio is used to reflect the relative binding strength of the probe to the two species of bacteria. The probes that bind five times more strongly to the *N. gonorrhoeae* test dots than to the *N. meningitidis* test dots, *i.e.*, having a binding ratio of 5, are the subject of Lo's invention (see, Lo, column 10, lines 45-57). The three nucleic acid probes deposited with the ATCC by Lo each hybridized to 20 strains of *N. gonorrhoeae*, but none of the 10 strains of *N. meningitidis* (see Lo, column 13, lines 20-26).

Lo does not teach obtaining the specific nucleotide sequence information for either the probes or test dots, nor does Lo provide any motivation to do so. For example, Lo teaches that three exemplary discrete nucleotide sequences specific to *N. gonorrhoeae* species, ATCC 53409, ATCC 53410, and ATCC 53411, were identified and deposited with the ATCC in the form of a recombinant DNA molecule. The lengths of these discrete nucleotide sequences were characterized, but no specific nucleotide sequence information was obtained (see, Lo, column 13, lines 9-60). Lo does not teach the specific nucleotide sequence information for either probes or test dots because such information is not necessary to Lo, as discussed above. On the contrary, Lo teaches away from obtaining and

using sequence information in its method for selecting probes by pointing out the laborious and time-consuming nature of the sequencing process (see Lo, column 3, lines 39-46). Therefore, there is no motivation for a skilled artisan to practice the teaching of Lo and to go through the laborious process of obtaining sequence information for either the probes or the immobilized DNA fragments in the test dots when such information is completely unnecessary to Lo's disclosed method.

Furthermore, Appellant respectfully submit that combining the teaching of the Lockhart Article with Lo adds little or no value to Lo or renders the invention of Lo useless, and destroys the disclosed advantage of Lo that is the avoidance of needing sequence information. The Examiner states that the Lockhart Article teaches probe design and "and provides details including starting with probes of known sequence (page 1680, left column, second full paragraph, lines 1-7)" (see Answer at page 14, third paragraph). The Lockhart Article provides that: "[t]he arrays are designed based on sequence information alone and are synthesized in situ using a combination of photolithography and oligonucleotide chemistry" (see, the Lockhart Article at page 1675, abstract). As such, in order to apply the methods of the Lockhart Article to Lo, one would need to have the sequence information of the genome of the organism being studied. However, in Lo, the relative binding ratio of a probe to the two types of test dots is determined by quantifying an amount of radioactivity that corresponds to the quantity of the probe. Knowing the sequence information of the probe provides little or no use to the teaching of Lo. Moreover, as discussed above, Lo clearly indicates that an advantage of its method is the avoidance of obtaining or using such sequence information (see Lo at column 3, lines 39-46). Lo emphasizes the point by implying that sequencing of an *N. meningitides* genome and of the genome of just one strain of *N. gonorrhoeae* would not even be sufficient, since in order for a sequence "to be useful as a polynucleotide probe it is essential that it be specific for other strains of *Neisseria gonorrhoeae* as well" (Lo, column 3, lines 30-45). Thus, Lo's method avoids the sequencing of multiple strains of *N. gonorrhoeae*. Adding the use of sequence information to Lo's method would destroy one of its conveyed advantages, and thus there is no motivation for such combination, making the combination nonobvious. See, *e.g.*, *In re Gordon*, 733 F.2d 900 (Fed. Cir. 1984).

Furthermore, if the necessary sequence information were available, such that the nucleotide sequences of the probes and the genomes for multiple strains of *N. gonorrhoeae* and for *N. meningitides* were known, the method of Lo would be rendered unnecessary

because the sequences of the strains in the two different species could be aligned and compared using computer software (*e.g.*, the GCG Wisconsin Package, which was available since the 1990's) to identify DNA segments that could serve as probes and that are present in the strains of *N. gonorrhoeae* but are not present in the strains of *N. meningitidis*. It therefore runs counter to common sense to presume that a skilled artisan would use the sequence information as described in the Lockhart Article in the context of Lo.

As such, neither Lo nor Lockhart provides any motivation to a person skilled in the art to combine the teachings of these references as proposed by the Examiner, and thus the combination is improper. Accordingly, Appellant respectfully submits that neither Lo nor Lockhart, alone or in combination renders the rejected claims obvious.

Second Sample

The Examiner's also contends that "Lo teaches ... the second sample comprises a plurality of different polynucleotides (i.e. chromosomal DNA from *N. meningitidis*, strains 53415, 53416, 53417, 53418 and 53419 and chromosomal DNA from *N. gonorrhoeae*, 53420, 53421,53422,53423, 53424, 53425) wherein at least 75% of the polynucleotide molecules in the first sample comprise the target sequence i.e. the molecules in the first sample comprise chromosomal DNA from strain 53414 (i.e. the target sequence) (Claim 1) (see Answer at page 15, second paragraph). Appellant respectfully disagrees.

Appellant respectfully points out that the Examiner's definition of the second sample is erroneous. Lo does not teach a second sample that "comprises a plurality of different polynucleotides (i.e. chromosomal DNA from *N. meningitidis*, strains 53415, 53416, 53417, 53418 and 53419 and chromosomal DNA from *N. gonorrhoeae*, 53420, 53421,53422,53423, 53424, 53425)" (see Answer at page 15, second paragraph), thus a mixture of DNA from different species or strains. Instead, Appellant submits that Lo's first sample consists of chromosomal DNA from *N. gonorrhoeae* while Lo's second sample consists of chromosomal DNA from *N. meningitidis*. For example, Lo clearly teaches that "[e]ach of the test dots consists of denatured purified chromosomal DNA isolated from ***one*** of the following strains of *Neisseria gonorrhoeae* and *Neisseria meningitidis* ..." (see, Lo, at column 8, lines 13-19, emphasis added). Because the test dots serve as references to identify a probe that distinguishes between *N. gonorrhoeae* and *N. meningitidis*, it is imperative that a test dot contain chromosomal DNA from a strain of ***only one*** of the species. As shown in the table from Lo at column 8, lines 20-29, the first sample (*i.e.*, the

left column of the table) is a test dot containing chromosomal DNA from one of six strains of the *N. gonorrhoeae* species (see Lo, claim 1, step (b)). The second sample (*i.e.*, the right column of the table) is a test dot containing chromosomal DNA from one of six strains of the *N. meningitidis* species (see Lo, claim 1, step (c)). Lo further provides that "***each*** strain of *Neisseria gonorrhoeae* and *Neisseria meningitidis* should have six test dots with each test dot for each strain being serially diluted by a factor of 10" (see, Lo, at column 11, lines 30-32, emphasis added). Therefore, the Examiner's contention regarding the second sample in Lo is erroneous.

First Sample Comprising 75% Target Sequence

The Examiner contends that "[a]ny nucleic acid sequence within the genomic fragments that hybridize to the probes is encompassed by the broadly claimed 'target sequence' and probes that are hybridizable thereto" (Answer, at page 15, first paragraph). The Examiner also contends that "at least 75% of the polynucleotide molecules in the first sample [of Lo] comprise the target sequence i.e. the molecules in the first sample comprise chromosomal DNA from strain 53414 (i.e. the target sequence) (claim 1)" (Answer, at page 15, second paragraph). Appellant respectfully disagrees for the following reasons.

In view of the language of claim 27 of the instant application, a target nucleotide sequence of the instant group of claim has to have at least a portion of it (termed for efficiency herein "the Relevant Sequence") that is complementary and hybridizable to the probe ("said polynucleotide probe comprising a predetermined nucleotide base sequence that is complementary to at least a hybridizable portion of said target nucleotide sequence;" (claim 27, lines 2-4)); the Relevant Sequence thus must be sufficiently long to mediate hybridization. This same Relevant Sequence must be present in at least 75% of the polynucleotide molecules in the first sample since "at least 75% of the polynucleotide molecules in said first sample are polynucleotide molecules comprising said target nucleotide sequence" (claim 27, lines 14-15). The Examiner's contention that Lo discloses a first sample with at least 75% of the polynucleotide molecules therein comprising the target sequence is based on the Examiner's allegation that the chromosomal DNA from strain 53414 is the target sequence. This allegation is unclear to Appellant, and can be interpreted in different ways: first, the entire intact chromosomal DNA from strain 53414 is alleged to be the target sequence; second, a fragment from the chromosomal DNA from strain 53414 is alleged to be the target sequence. Appellant shows that, under both

interpretations, the Examiner's contention that Lo discloses that at least 75% of the first sample comprises the target sequence is erroneous.

First, Appellant addresses the contention that the entire chromosomal genomic DNA of strain 53414 is the target sequence. Clearly, if such were the case, none of the test dots in Lo meets the limitations of the first sample of claim 27 of the instant application, since the polynucleotide molecules in the test dots are *fragments* of chromosomal DNA; thus, *none* of the molecules in the test dots comprises (consists of at least) the entire chromosomal DNA, much less 75% of the molecules in any of the test dots. The transitional term "comprising" is an open-ended term construed as "containing at least." See *Genentech Inc. v. Chiron Corp.*, 112 F.3d 495, 501 (Fed. Cir. 1997) ("'Comprising' is a term of art used in claim language that means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim.")

Second, even if the Examiner were alleging that a specific fragment of the chromosomal DNA from strain 53414 is the target sequence, Lo still does not disclose the first sample of the instant claims. Appellant provides the following example to illustrate that, even under this scenario, the Examiner's contention regarding the first sample is still erroneous. As discussed above, Lo teaches first and second samples that contain randomly generated fragments. Molecules in the first sample can be generated by randomly fragmenting the chromosomal DNA from strain 53414 of *N. gonorrhoeae*. As such, the randomly generated DNA fragments together constitute the entire genome of strain 53414 of *N. gonorrhoeae*. If, as the Examiner contends, 75% of the molecules in the first sample in Lo comprise a target sequence (containing the Relevant Sequence) from the chromosomal DNA from strain 53414 of *N. gonorrhoeae*, 75% of such molecules have to contain at least the same hybridizable sequence ("the Relevant Sequence"). There is no teaching, suggestion, or expectation that this would occur; since the test dots contain randomly generated fragments, it is unreasonable to expect that at least 75% of the polynucleotide molecules in a test dot would contain the same hybridizable sequence.

Therefore, Appellant respectfully submits that, under both possible interpretations, the Examiner's contention, that at least 75% of the polynucleotide molecules in the first sample of Lo comprise the target sequence, is erroneous.

Hindsight Reasoning

As discussed previously under "Motivation to Combine," there is no evidence to support that one skilled in the art will be motivated to combine the teaching of Lo with that of the Lockhart Article, and the Examiner's contention that Lockhart clearly provides such motivation has been shown to have no merit. Therefore, Appellant respectfully submits that such contention of motivation to combine is clearly hindsight reasoning.

Accordingly, the Examiner's response to Appellant's argument relating to claims 27, 29-30, 33-40, 42-54, 59-60, 64-65, 67, 73 and 90-104 is erroneous, and the rejection should be reversed.

The Examiner's Misunderstanding of Appellant's Statement

On page 16, second paragraph, of the Examiner's Answer, the Examiner states that "Appellant appears to be asserting that the claimed 'plurality of different polynucleotide molecules' is defined as molecules from different sources." This is incorrect. Appellant was not asserting such an interpretation of the claims; rather, Appellant was correcting the Examiner's mischaracterization of Lo as teaching that each dot comprises a mixture of chromosomal DNA from two or more strains (see Appeal at page 22, second paragraph and Office Action dated January 13, 2006 at page 4, last paragraph, bridging to page 5).

The Examiner's Response to Appellant's Argument B2 Relating to Claims 27, 29-30, 33-40, 42-67, 73-75, 84-85, and 90 Is Erroneous

In response to Appellant's argument B2 relating to claims 27, 29-30, 33-40, 42-67, 73-75, 84-85, and 90, the Examiner contends that:

> Lo et al. teach the molecules in the first sample comprise chromosomal DNA from strain 53414 (i.e. the target sequence) (Claim 1). Because the target sequence is broadly defined as having a hybridizable sequence and because Lo et al. teach hybridizable chromosomal DNA in each spot, Lo et al teach the target sequence-containing molecules as broadly claimed

See Answer at page 16, third paragraph. Appellant respectfully disagree.

Appellant respectfully points out that a target sequence as claimed is not ***any*** hybridizable sequence. As explained above, it is a particular sequence comprising the Relevant Sequence, which per this group of claims, must be present in at least 75% of the polynucleotide molecules in the first sample.

The first sample as taught by Lo is not a sample in which at least 75% of the molecules comprise the target sequence as specified in the claims of the instant application, as discussed above and reiterated below.

In view of the language of claim 27 of the instant application, a target nucleotide sequence of the instant group of claims has to have at least a portion of it (termed for efficiency herein "the Relevant Sequence") that is complementary and hybridizable to the probe ("said polynucleotide probe comprising a predetermined nucleotide base sequence that is complementary to at least a hybridizable portion of said target nucleotide sequence;" (claim 27, lines 2-4)); the Relevant Sequence thus must be sufficiently long to mediate hybridization. This same Relevant Sequence must be present in at least 75% of the polynucleotide molecules in the first sample since "at least 75% of the polynucleotide molecules in said first sample are polynucleotide molecules comprising said target nucleotide sequence" (claim 27, lines 14-15). The Examiner's contention that Lo discloses a first sample with at least 75% of the polynucleotide molecules therein comprising the target sequence is based on the Examiner's allegation that the chromosomal DNA from strain 53414 is the target sequence. This allegation is unclear to Appellant, and can be interpreted in different ways: first, the entire intact chromosomal DNA from strain 53414 is alleged to be the target sequence; second, a fragments from the chromosomal DNA from strain 53414 is alleged to be the target sequence. Appellant shows that, under both interpretations, the Examiner's contention that Lo discloses that at least 75% of the first sample comprises the target sequence is erroneous.

First, Appellant addresses the contention that the entire chromosomal genomic DNA of strain 53414 is the target sequence. Clearly, if such were the case, none of the test dots in Lo meets the limitations of the first sample of claim 27 of the instant application, since the polynucleotide molecules in the test dots are *fragments* of chromosomal DNA; thus, *none* of the molecules in the test dots comprises (consists of at least) the entire chromosomal DNA, much less 75% of the molecules in any of the test dots. The transitional term "comprising" is an open-ended term construed as "containing at least." See *Genentech Inc. v. Chiron Corp.*, 112 F.3d 495, 501 (Fed. Cir. 1997) ("'Comprising' is a term of art used in claim language that means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim.")

Second, even if the Examiner were alleging that a specific fragment of the chromosomal DNA from strain 53414 is the target sequence, Lo still does not disclose the

first sample of the instant claims. Appellant provides the following example to illustrate that, even under this scenario, the Examiner's contention regarding the first sample is still erroneous. As discussed above, Lo teaches first and second samples that contain randomly generated fragments. Molecules in the first sample can be generated by randomly fragmenting the chromosomal DNA from strain 53414 of *N. gonorrhoeae*. As such, the randomly generated DNA fragments together constitute the entire genome of strain 53414 of *N. gonorrhoeae*. If, as the Examiner contends, 75% of the molecules in the first sample in Lo comprise a target sequence (containing the Relevant Sequence) from the chromosomal DNA from strain 53414 of *N. gonorrhoeae*, 75% of such molecules have to contain at least the same hybridizable sequence ("the Relevant Sequence"). There is no teaching, suggestion, or expectation that this would occur; since the test dots contain randomly generated fragments, it is unreasonable to expect that at least 75% of the polynucleotide molecules in a test dot would contain the same hybridizable sequence.

Therefore, Appellant respectfully submits that, under both possible interpretations, the Examiner's contention that at least 75% of the polynucleotide molecules in the first sample of Lo comprise the target sequence is erroneous.

Accordingly, the Examiner's response to Appellant's argument B2 relating to claims 27, 29-30, 33-40, 42-67, 73-75, 84-85, and 90 is erroneous, and the rejection should be reversed.

The Examiner's Response to Appellant's Argument B3 Relating to Claims 29, 37, 39, 42, 92 and 94 Is Erroneous

In response to Appellant's argument relating to claims 29, 37, 39, 42, 92 and 94, the Examiner contends that claim 29 defines the target as "any nucleotide sequence (e.g. 2 nucleotides) from a gene sequence," and that "[t]he claims do not require that the target nucleotide sequence be a known sequence of nucleotides. The claims merely require probes have a known nucleotide sequence, a portion of which is hybridizable to the target" (Answer, first paragraph, page 17). Appellant respectfully disagrees for the following reasons.

Claim 29 depends from claim 27, which recites "a polynucleotide probe to a target nucleotide sequence, said polynucleotide probe comprising a predetermined nucleotide base sequence that is complementary to at least a hybridizable portion of said target nucleotide

sequence." Because the predetermined nucleotide base sequence is ***complementary*** to at least a hybridizable portion of the target nucleotide sequence, by definition of the concept of complementarity, the nucleotide sequence of the hybridizable portion of the target nucleotide sequence is also known (this is true since the complement of any known sequence is thereby known in view of known Watson-Crick hybridization rules. Thus, for example, the complement of 5′-AGC-3′ is 5′-GCT-3′). Accordingly, the target nucleotide sequence contains a sequence of known nucleotide base sequence that is complementary to and of sufficient length to hybridize to the probe.

Therefore, the Examiner's contention that the target nucleotide sequence is defined as "any nucleotide sequence (e.g. 2 nucleotides) from a gene sequence," and that "the claims do not require that the target nucleotide sequence be a known sequence of nucleotides" is erroneous.

As discussed in the Appeal, claims 29, 37, 39, 42, 92 and 94 have the additional limitation that the target polynucleotide sequence is a nucleotide sequence from a gene or gene transcript of a cell or organism or an mRNA, cDNA or cRNA derived therefrom (claim 29) or a nucleotide sequence from a gene or gene transcript of a cell or organism (claims 37, 39, 42, 92 and 94)[1]. As such, the target nucleotide sequence in claims 29, 37, 39, 42, 92 and 94, containing the Relevant Sequence, is not from an intergenic region of a genome. In Lo, the test dots contain randomly generated fragments of chromosomal DNA, which chromosomal DNA contains both gene and non-gene sequences. There is no teaching, suggestion, or expectation from Lo that the particular sequence to which a probe of Lo hybridizes is from a gene or gene transcript as opposed to an intergenic chromosomal DNA region, much less that 75% of the polynucleotide molecules in a test dot would contain the same hybridizable gene transcript sequence.

Therefore, the Examiner's response to Appellant's argument B3 relating to claims 29, 37, 39, 42, 92 and 94 is erroneous, and the rejection should be reversed.

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[1] Claims 39 and 94 recite "comprises" instead of "is."

The Examiner's Response to Appellant's Argument B4 Relating to Claims 37, 39, 42, 92 and 94 Is Erroneous

In response to Appellant's argument B4 relating to claims 37, 39, 42, 92 and 94, the Examiner contends that:

> Lo et al teach their method screens closely related samples to analyze probe-specific probes (Column 3, lines 30-39) wherein their method provides for screening nucleotide sequences that are specific for a "genetically distinct group" (Column 4, lines 15- 17 and 18-42). Which clearly suggests their method is useful for wild-type and mutants (e.g. deletion mutants). Hence, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the method of Lo et al to screen genetically distinct groups (e.g. mutants and/or wild-type samples) to thereby screen and analyze mutants and/or wild-type-specific probes as they suggest (Column 3, lines 30-39 and Column 4, lines 15-17).

See Answer at page 17, second paragraph). Appellant respectfully disagrees for the reasons discussed in subsections A and B below.

A. Claims 37, 42, and 92

Claims 37, 42 and 92 specify that the target nucleotide sequence is a sequence from a gene or gene transcript of a cell or organism, and that the second sample comprises a polynucleotide sample from a *deletion mutant* of the cell or organism. Appellant respectfully points out that "genetically distinct group" in Lo refers to a particular species within the genus of *Neisseria*, *i.e.*, specific for *Neisseria gonorrhoeae* as opposed to *Neisseria meningitidis* (see, for example, Lo, at column 1, lines 11-13; column 2, lines 59-62; and column 3, lines 49-55). The genetically distinct groups referred to by Lo are clearly different *Neisseria* species. There is absolutely no hint or suggestion in Lo of screening probes for other than the ability to distinguish between different *Neisseria* species; that is, there is no teaching of hybridization to any sample with polynucleotides from a deletion mutant not expressing the gene or gene transcript which the target polynucleotide sequence is from.

Therefore, the Examiner's response to Appellant's argument B4 relating to claims 37, 42, and 92 is erroneous, and the rejection should be reversed.

B. Claims 39, 42, 92, and 94

Claims 39, 42, 92, and 94 specify the target nucleotide sequence comprises or is a sequence from a gene or gene transcript of a cell or organism, and that the second sample (in the case of claims 39 and 94) or the first sample (in the case of claims 42 and 92) comprises a polynucleotide sample from a *wild type* strain of the cell or organism that expresses the gene or gene transcript. Appellant respectfully points out that "genetically distinct group" in Lo refers to a particular species within the genus of *Neisseria, i.e.*, specific for *Neisseria gonorrhoeae* as opposed to *Neisseria meningitidis* (see, for example, Lo, at column 1, lines 11-13; column 2, lines 59-62; and column 3, lines 49-55). The genetically distinct groups referred to by Lo are clearly different *Neisseria* species. There is absolutely no hint or suggestion in Lo of screening probes for other than the ability to distinguish between different *Neisseria* species; that is, there is no teaching of hybridization to any sample with polynucleotides from a wild type strain known to express the gene or gene transcript which the target polynucleotide sequence is from.

Therefore, the Examiner's response to Appellant's argument B4 relating to claims 39, 42, 92 and 94 is erroneous, and the rejection should be reversed.

The Examiner's Response to Appellant's Argument B5 Relating to Claims 36, 40 and 91-92 Is Erroneous

In response to Appellant's argument B5 relating to claims 36, 40 and 91-92, the Examiner contends that:

> both references teach the second sample does not contain the broadly claimed target i.e. Lo et a1 teach the second sample does not comprise the target (i.e. chromosomal DNA from *N. gonorrhoeae*) but instead comprises chromosomal DNA from *N. meningitidis* (Column 8, lines 13-28) and Lockhart et al teach the molecules of the second sample do not comprise the target i.e. complex RNA, not cytokine RNA (page 1680, left column).

See Answer, third paragraph, at page 17, bridging to first paragraph, at page 18.

Appellant first respectfully points out that the Examiner's assertion of "Lo et al teach the second sample does not comprise the target (i.e. chromosomal DNA from *N. gonorrhoeae* but instead comprise chromosomal DNA from *N. meningitidis* (Column 8, lines 13-28)" (Answer, third paragraph, at page 17, bridging to first paragraph, at page 18)

is inconsistent with the Examiner's assertion of "the second sample comprises a plurality of different polynucleotides (i.e. chromosomal DNA from *N. meningitidis*, strains 53415, 53416, 53417, 53418 and 53419 and chromosomal DNA from *N. gonorrhoeae*, 53420, 53421,53422,53423, 53424, 53425)" (Answer, second paragraph, at page 15).

Claims 36, 40, 91 and 92 have the additional limitation that the different polynucleotide molecules in the second sample do not comprise the target nucleotide sequence. Appellant has previously stated the reasons why this group of claims is nonobviousness (see Appeal at pages 29-30).

Accordingly, the Examiner's response to Appellant's argument B5 relating to claims 36, 40 and 91-92 is erroneous, and the rejection should be reversed.

The Examiner's Response to Appellant's Argument B6 Relating to Claim 38 Is Erroneous

In response to Appellant's argument B6 relating to claim 38, the Examiner contends that:

> Lo et al teach the second sample comprises chromosomal DNA from different *N. meningitidis* strains and from *N. gonorrhoeae* strains (Column 8, lines 13-28). Lo et al teach that the *N. meningitidis* strains do not comprise the target while the *N. gonorrhoeae* strains do comprise the target as evidenced by the *N. gonorrhoeae* detection taught by Lo et al (Column 10, line 51-Column 12, line 65) and Lockhart *et al.* teach the similar method wherein the second sample comprises the claimed different molecules i.e. 'all known genes' from the organism (page 1680, left column). Furthermore, Lockhart specifically teaches the second sample is used to determine which probes 'were poor or promiscuous hybridizers,' (page 1680, left column second full paragraph, lines 14-20) thereby providing the motivation for using the second sample as claimed.

See Answer, second paragraph, at page 18.

Appellant again respectfully points out that the Examiner's definition of the second sample has been inconsistent. As quoted above in response to Appellant's argument B6 relating to claim 38, the Examiner contends that "Lo et al teach the second sample comprises chromosomal DNA from different *N. meningitidis* strains and from *N. gonorrhoeae* strains" (Answer, second paragraph, at page 18). However, previously in response to Appellant's argument B5 relating to claims 36, 40 and 91-92, the Examiner contends that "Lo et al teach the second sample does not comprise the target (i.e.

chromosomal DNA from *N. gonorrhoeae*) but instead comprises chromosomal DNA from *N. meningitidis* (Answer, third paragraph, page 17). Appellant respectfully points out that Lo's first sample consists of chromosomal DNA from *N. gonorrhoeae* while Lo's second sample consists of chromosomal DNA from *N. meningitidis*. Lo does not teach any sample that "comprises chromosomal DNA from different *N. meningitidis* strains and from *N. gonorrhoeae* strains." For example, Lo clearly teaches that "[e]ach of the test dots consists of denatured purified chromosomal DNA isolated from one of the following strains of *Neisseria gonorrhoeae* and DNA from *Neisseria meningitidis* ..." (see, Lo, at column 8, lines 13-19).

With respect to claim 38, this claim has the additional limitation that the different polynucleotide molecules in the second sample comprise both polynucleotide molecules comprising the target nucleotide sequence and a plurality of different polynucleotide molecules that do not comprise the target nucleotide sequence. Thus, the method as claimed by claim 38 evaluates a binding property of a probe having a predetermined sequence by determining a ratio of hybridization of the probe to a first sample that comprises polynucleotide molecules comprising the target sequence, and a second sample that comprises both polynucleotide molecules that comprise the target sequence and a plurality of different polynucleotide molecules not comprising the target sequence. Lo does not teach or suggest that any of the polynucleotide molecules in its second sample, *i.e.*, test dots of *N. meningitidis*, comprise both polynucleotide molecules that comprise the target sequence and a plurality of different polynucleotide molecules not comprising the target sequence. Appellant also respectfully points out that Lo's method is designed to identify probes that are specific to *N. gonorrhoeae* but not *N. meningitidis*, two bacteria having a high degree of DNA homology (see, e.g., Lo at col. 2, lines 58-61). A person skilled in the art would not be motivated to modify Lo's method such that its second sample comprises both polynucleotide molecules that comprise the target sequence and polynucleotide molecules that do not comprise the target sequence of the probe.

Moreover, if the Examiner is contending that, although Lo does explicitly not teach that the second sample comprises both polynucleotide molecules that comprise the target sequence and a plurality of different polynucleotide molecules not comprising the target sequence, it is inevitable that such polynucleotide molecules exist in Lo's second sample, for example, in view of the nucleotide molecules that are homologous between *N. gonorrhoeae* and *N. meningitidis*, the Examiner's rejection must fail. It is not inevitable

that the *N. meningitidis* test dots that exhibit some level of hybridization to the probe contain polynucleotide sequences comprising the target nucleotide sequence (as well as ones that do not comprise the target sequence), since the target nucleotide sequence contains a particular sequence ("the Relevant Sequence") which, as discussed above, is hybridizable and complementary to the probe, and which must be present in the first sample (the *N. gonorrhoeae* test dot) if one is attempting to meet the limitation of claim 38 (since the first sample contains molecules comprising the target sequence). However, hybridization of such a *N. meningitidis* test dot to the probe *may* be accounted for by cross-hybridization of sequences similar but not identical to the Relevant Sequence. Thus, it is not inevitable that the hybridizable sequences in the *N. gonorrhoeae* test dot are the same as the hybridizable sequences in the *N. meningitidis* test dot.

Thus, it is not inevitable that such *N. gonorrhoeae* test dots contain molecules comprising the target sequence. To the extent that the Examiner is contending that Lo inherently discloses the second sample of the above group of claims, such a contention is an improper basis for the rejection. Firstly, an obviousness rejection under U.S.C § 103 cannot be based on inherent disclosure in a prior art reference. The Court of Customs and Patent Appeals has stated that "the inherency of an advantage and its obviousness are entirely different questions. That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown." *In re Spormann*, 363 F.2d 444, 448 (C.C.P.A. 1966). Secondly, even where inherent anticipation can properly be considered (which is not the instant case), it is well established that in order for a prior art reference to amount to an inherent anticipation of a claim, all the elements of the claim must *necessarily*, *inevitably*, and *always* result from the prior art disclosure and would be so recognized by one of ordinary skill in the art; mere possibilities or probabilities are not sufficient. *See Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1269 (Fed. Cir. 1991); *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553-1554 (Fed. Cir. 1983); *In re Oelrich*, 666 F.2d 578, 581 (C.C.P.A. 1981); *Phillips Petroleum Co. v. U.S. Steel Corp.*, 673 F.Supp. 1278, 1295 n.12 (D. Del. 1987), *aff'd*, 865 F.2d 1247 (Fed. Cir. 1989); *Hughes Aircraft Co. v. U.S.*, 8 U.S.P.Q.2d 1580, 1583 (Ct. Cl. 1988); *Ex parte Levy*, 17 U.S.P.Q.2d 1461, 1463-64 (B.P.A.I. 1990); *Ex parte Skinner*, 2 U.S.P.Q.2d 1788, 1788-89 (B.P.A.I. 1987). Thus, it is not sufficient that a teaching of a prior art reference *could* yield a result that would anticipate the claim against which the prior art reference is applied; instead, to be

anticipatory under the doctrine of inherency, the teaching of the prior art reference *must inevitably* lead to the result.

The Examiner also contends that "Lockhart et a1 teach the similar method wherein the second sample comprises the claimed different molecules i.e. 'all known genes' from the organism (page 1680, left column)" (see Answer at page 18, second paragraph). Appellant respectfully points out that the Examiner has mischaracterized the teaching of the Lockhart Article. The section of the Lockhart Article to which the Examiner refers is aimed at selecting probe sequences that are unique for a specific gene. Specifically, the Lockhart Article provides:

> The oligonucleotides probes ... were selected from 600 bases of sequence at the 3′ end ... of each RNA.... Further selection was based on the criteria of uniqueness and hybridization characteristics. Uniqueness was assessed narrowly by comparing potential probe sequences with the full-length sequences of the other murine genes being monitored, and rejecting those that matched at 17 or more positions (allowing loops of up to three bases). A search of this type can be made more global by comparing probe sequences with the sequence of *all known genes* of a particular organism.

(Lockhart Article at page 1680, left column, emphasis added). As such, the reference to "all known genes" in the Lockhart Article is in no way suggests that such all known genes were used in a hybridization sample. Instead, the reference describes a process that compares potential probe sequences with the sequences of all known genes of a particular organism and subsequently rejects the probes with too many matches to different genes. As such, the Lockhart Article does not disclose a sample of all known genes as alleged by the Examiner.

The Examiner further contends that "Lockhart specifically teaches the second sample is used to determine which probes 'were poor or promiscuous hybridizers,' (page 1680, left column second full paragraph, lines 14-20) thereby providing the motivation for using the second sample as claimed" (Answer, second paragraph, at page 18).

This section of the Lockhart Article referred to by the Examiner states that:

> Pools of specific cytokine RNAs were hybridized under stringent conditions to the 16,000 probe murine cytokine arrays. Additionally, complex RNA populations that did not contain the cytokine RNAs were used to hybridized to the same arrays. These two types of experiments were used to determine which probes hybridized strongly and specifically, and which ones were poor or promiscuous hybridizers.

(Lockhart Article at page 1680, left column). Thus, a first sample, containing specific cytokine RNAs, as disclosed in the Lockhart Article, contains the target sequences to which the probes in the murine cytokine array bind, and a second sample, containing complex RNA but not containing the cytokine RNAs, as disclosed in the Lockhart Article, does not contain the target sequences to which the probes in the murine cytokine array bind; this clearly differs from claim 38 of the instant application which specifies that both the first and second sample contain polynucleotide molecules comprising the target sequence (in view of the language of claim 27, upon which claim 38 depends).

Thus, Lo and the Lockhart Article do not teach or suggest a method of evaluating a binding property of a probe by determining a ratio of hybridization of a probe between a first sample and a second sample, wherein the second sample contains polynucleotide molecules comprising the target nucleotide sequence, and different polynucleotide molecules that do not comprise the target nucleotide sequence, and claim 38 is separately patentable.

Accordingly, the Examiner's response to Appellant's argument B6 relating to claim 38 is erroneous, and the rejection should be reversed.

The Examiner's Response to Appellant's Argument B7 Relating to Claims 43-54 and 95-104 Is Erroneous

In response to Appellant's argument B7 relating to claims 43-54 and 95-104, the Examiner contends that "the claims merely require probes have a known nucleotide sequence, a portion of which is hybridizable to the target. Hence, Appellants arguments regarding known target sequence are not commensurate in scope with the claims." (Answer, third paragraph, page 18). Appellant respectfully disagrees.

With respect to claims 43-54 and 95-104, these claims each have an additional limitation specifying specific relative abundance of polynucleotides comprising the target sequence and polynucleotides not comprising the target sequence, between the first sample and the second sample. Claims 43-54 depend directly or indirectly from claim 27, while claims 95-104 depend directly or indirectly from claim 93. As discussed above, claim 27 recites "a polynucleotide probe to a target nucleotide sequence, said polynucleotide probe comprising a predetermined nucleotide base sequence that is complementary to at least a hybridizable portion of said target nucleotide sequence." Because the predetermined

nucleotide base sequence is ***complementary*** to at least a hybridizable portion of the target nucleotide sequence, by definition of the concept of complementarity, the nucleotide sequence of the hybridizable portion of the target nucleotide sequence is also known (this is true since the complement of any known sequence is thereby known in view of known Watson-Crick hybridization rules. Thus, for example, the complement of 5′-AGC-3′ is 5′-GCT-3′). Accordingly, the target nucleotide sequence contains a sequence of known sequence that is complementary to and of sufficient length to hybridize to the probe.

Claims 43-54 depend ultimately from claim 27. Therefore, the Examiner's contention that "the claims merely require probes have a known nucleotide sequence, a portion of which is hybridizable to the target," and that "Appellants arguments regarding known target sequence are not commensurate in scope with the claims" is erroneous in view of claims 43-54.

Similarly, claim 93 recites "each polynucleotide probe in the plurality of polynucleotide probes comprises a different predetermined nucleotide base sequence that is complementary to at least a hybridizable portion of said target nucleotide sequence." As discussed above, because the predetermined nucleotide base sequence is ***complementary*** to at least a hybridizable portion of the target nucleotide sequence, by definition of the concept of complementarity, the nucleotide sequence of the hybridizable portion of the target nucleotide sequence is also known. Accordingly, the target nucleotide sequence contains a sequence of known sequence that is complementary to and of sufficient length to hybridize to the probe.

Claims 95-104 depend ultimately from claim 93. Therefore, the Examiner's contention that the target is defined as "the claims merely require probes have a known nucleotide sequence, a portion of which is hybridizable to the target," and that "Appellants arguments regarding known target sequence are not commensurate in scope with the claims" is erroneous in view of claims 95-104.

The Examiner further contends that:

> Lo et a1 teach the method wherein the first sample further comprises molecules that do not comprise the target e.g. chromosomal regions homologous between *N. meningitidis* and *N. gonorrhoeae* (Column **3,** lines 10-30) and the second sample comprises polynucleotides comprising the target and a plurality of different polynucleotides comprising different sequences, not the target. In this embodiment the first and second samples each comprises sample spots of *N. meningitidis* and sample spots of *N. gonorrhoeae* wherein the first sample spots have 500

> nanograms chromosomal DNA and the second sample spots have 5 picograms of chromosomal DNA thereby providing amounts of polynucleotides differing by at least a factor of 100 (Column 11, lines 29-42).... Lo et al also teaches the probe evaluation method wherein the amount/abundance of polynucleotide in the first sample is the same as the amount/abundance in the second sample (Column 11, lines 29-42) and therefore differs by no more than a factor of two of by no more than 1% as claimed.

Answer, page 18, third paragraph, bridging to page 19. Appellant respectfully disagrees for the following reasons.

While the Examiner's contention is unclear, Appellant understands the Examiner to be contending that the target sequence is a chromosomal region homologous between *N. meningitidis* and *N. gonorrhoeae*, and that thus both the first and second samples of Lo contain molecules comprising, and molecules not comprising, the target sequence. As discussed above, the target sequence is a sequence that contains a particular, known sequence ("the Relevant Sequence") that is complementary to and of sufficient length to hybridize to the probe. The Examiner's contention regarding the relative amounts of chromosomal DNA in the test dots of Lo bears no relation to the relevant amounts of the polynucleotide molecules comprising or not comprising the target sequence specified in the instant claims. The relationship between the total amount of DNA in the test dots and the amount of polynucleotide molecules in the test dots that contain (or, alternatively, do not contain) the target sequence is unknown. Thus, the relative amounts of total DNA in the test dots give no hint or suggestion of the relative amounts of the molecules in the test dots that contain (or, alternatively, do not contain) the target sequence. Thus, there is no teaching or suggestion in Lo of the relative amounts specified in the claims. The Lockhart Article does not remedy this deficiency because it also does not teach or suggest samples with the relative amounts specified in the claims.

Accordingly, the Examiner's response to Appellant's argument B7 relating to claims 43-54 and 95-104 is erroneous, and the rejection should be reversed.

II. The Examiner's Response to Appellant's Argument C1-C3 Relating to Claims 61-63, 66, 74-75 and 84-85 Is Erroneous

With respect to claims 61-63, 66, 74-75 and 84-85 being rejected as being obvious over U.S. Patent No. 4,900,659 ("Lo") in view of Lockhart et al., Nature Biotechnology

14:1675-1680 ("the Lockhart Article") as applied to claims 27 and 67, and in further view of Lockhart et al., U.S. Patent No. 6,344,316 B1 ("the Lockhart Patent"), Appellant respectfully submits that the Examiner's Answer to Appellant's arguments C1-C3, as set forth in the Appeal, is erroneous.

Teaching of the Lockhart Patent

The Lockhart Patent teaches methods for identifying differences in nucleic acid abundances (*e.g.*, expression levels) between two or more samples using high density DNA microarrays. In the Lockhart Patent, a method of optimizing a set of probes for detection of a particular gene is disclosed. The probe optimization method involves first hybridizing the probes with their target nucleic acids alone and then hybridizing the probes with a high complexity, high concentration nucleic acid sample that does not contain the targets complementary to the probes (the Lockhart Patent, column 36, lines 30-36), and selecting those probes that show a strong hybridization signal with their target and little or no cross-hybridization with the high complexity sample as preferred probes for use in the high density arrays (the Lockhart Patent, column 36, lines 44-47). The Lockhart Patent then provides a detailed explanation of how the foregoing is accomplished. For selection of probes showing a strong hybridization signal with their target with the high complexity sample, the Lockhart Patent teaches that the probes are hybridized to a sample containing target nucleic acids having subsequences complementary to the oligonucleotide probes, and those probes are selected for which the difference in hybridization intensity between the perfect-match probes and their respective mismatch controls exceeds a threshold hybridization intensity (see, *e.g.*, the Lockhart Patent col. 37, lines 1-12). For selection of probes showing little or no cross-hybridization, the Lockhart Patent teaches that the probes can be hybridized with a nucleic acid sample that is not expected to contain sequences complementary to the probes, and those probes are selected for which both the probes and their mismatch controls show hybridization intensities below a threshold value (see, *e.g.*, the Lockhart Patent col. 37, lines 13-27). Thus, in the Lockhart Patent, selection of probes that show a strong hybridization signal with their target and little or no cross-hybridization is achieved by evaluating a probe according to its ability to hybridize to the target sample, and comparing this ability to a threshold, and separately, evaluating the probe according to its ability to hybridize to the non-target sample, and comparing this latter ability to a threshold. The Lockhart Patent does not teach or suggest comparing directly the hybridization signal

and cross-hybridization signal of the same probe, much less combining the hybridization signal and cross-hybridization signal of the same probe into a single quantity, *e.g.*, a ratio, and using such a single quantity as a measure of the binding property of the probe.

In the following, Appellant respectfully submits replies to the Examiner's Answer to Appellant's arguments C1-C3, in the same order as set forth in the Appeal.

The Examiner's Response to Appellant's Argument C1 Relating to Claims 61-63, 66, 74-75 and 84-85 Is Erroneous

Motivation to Combine

Appellant first respectfully submits that the Examiner's U.S.C. § 103 rejection of claims 61-63, 66, 74-75 and 84-85 being rejected as being obvious over Lo in view of the Lockhart Article as applied to claims 27 and 67, and in further view of the Lockhart Patent is erroneous because the Examiner has not satisfied her burden of establishing a prima facie case of obviousness.

As discussed in detail hereinabove in the section discussing the Examiner's response to Appellant's Argument B1, under the caption "Motivation to Combine," the Examiner's alleged motivation for combining the use of sequence information in the Lockhart Article with the method of Lo fails, and the Lockhart Article does not provide any such motivation. Appellant's remarks hereinabove under the caption "Motivation to Combine" are incorporated herein by reference in their entireties, and for brevity's sake are not repeated herein. The Examiner relies on the Lockhart Patent only for teaching the fluorescent labels and arrays of claims 61-63, 66, 74-75, and 84-85 (See Answer at page 19, second paragraph). Nevertheless, Appellant points out that the Lockhart Patent also does not supply any motivation for using sequence information in the method of Lo, since the Lockhart Patent, like the Lockhart Article, is concerned with large-scale expression analysis which is irrelevant to the purpose and concerns of Lo, and since Lo's method does not need sequence information, and the use of sequence information in Lo's method would add little or no value to Lo or render Lo's invention useless, and destroys a disclosed advantage of Lo (see above under the caption "Motivation to Combine").

As such, neither Lo nor the Lockhart Article nor the Lockhart Patent provides any motivation to a person skilled in the art to combine the teachings of these references as proposed by the Examiner, and thus the combination is improper.

The Examiner states that:

> Appellant asserts that "one skilled in the art would understand that there is not [sic] need to label the polynucleotides in Lo's sample, much less to label them differentially. In addition, a person skilled in the art would also understand that, in such a method, hybridization of a probe to different samples can be detected without the need of differential labeling, because the different samples, i.e., different test dots, are spatially addressable. Thus, a person skilled in the art would not be motivated to differentially label with fluorescent labels the polynucleotides of Lo." Appellant's comments are noted, however the comments assert opinions of "one skilled in the art". However, the asserted opinions appear to be unsupported by any evidence of such opinions. Therefore, the assertions are deemed opinion of counsel and not of one skilled in the art. Furthermore, as stated above the rejection, the differential labeling and array of the Lockhart Patent permit high-density array hybridization and differential detection very strong signal with low background as desired in the art (Column 24, lines 54-67; Column 36, lines 25-27; Column 37, lines 44-56).

See Answer at second paragraph, page 19. Appellant respectfully disagrees, for the reasons discussed in subsections A and B below.

A. Claims 61-63 and 84

Appellant respectfully points out that, in claims 61-63 and 84, it is polynucleotide molecules in a *sample*, not the *probe*, which are detectably labeled. The alleged samples of Lo, *i.e.*, the test dots disclosed in Lo, are differentiated based on spatial arrangement. That is, the test dots are arranged in a spatially addressable matrix, wherein location gives identity of the sample in the test dot; each sample that is hybridized is then detected by presence of the radio labeled probe at that location (see, for example, Lo at column 11, line 64, through column 12, line 3). As such, the identities of the different samples in Lo, *i.e.*, test dots, are defined and distinguished by spatial arrangement. This is a fact, not an opinion of counsel as alleged by the Examiner. Another fact is that differential labeling of molecules is used to distinguish the labeled molecules (see the Lockhart Patent at column 24, lines 59-67, which text is cited by the Examiner in the Office Action dated January 13, 2006 at page 13, first paragraph). It is clear that differential labeling of the different test dots, which would be done in order to distinguish the test dots, is not needed and is irrelevant to Lo's method since the test dots of Lo are already distinguished by spatial location. Also, there is no value to labeling either the first or second sample of Lo, much less to label them differentially, because the amount of probes bound (*i.e.*, the amount of

hybridization) to either the first or second sample is measured by the radioactivity present in the probes that are hybridized to either the first or second sample. Labeling either the first or second sample, on the other hand, would not provide such a measurement of the amount of probe bound. The first and second samples, as taught by Lo, comprise chromosomal DNAs, at set quantities in serial dilution, that are immobilized on matrices as test dots (see Lo at column 11, lines 29-42). Were the DNA fragments of the first and second samples to be labeled, the signals in these labels would provide a measurement only of the DNA in the test dot (the amount of which is already known), not the amount of probes that are bound to the test dots in the matrices. Therefore, labeling the first and second samples in Lo provides no value. As such, one skilled in the art will not be motivated to combine the teaching of the Lockhart Patent with that of Lo. If a teaching is unnecessary and irrelevant, it is clear that there is no motivation to incorporate such teaching. A person skilled in the art would understand that there is no value to labeling the polynucleotides in Lo's samples, much less to label them differentially. It is the Examiner's burden to provide evidence of motivation to combine the teaching of the cited references in order to make a prima facie obviousness rejection. This she has not done.

Accordingly, the Examiner's response to Appellant's argument C1 is erroneous, and the rejection of claims 61-63 and 84 should be reversed.

B. Claims 66 and 74

Claims 66 and 74 specify that the polynucleotide probe or probes is/are one of a plurality of polynucleotide probes comprising probes in an array. The Examiner's statements in the Answer in response to Appellant's argument regarding these claims are quoted hereinabove. The Examiner is citing the Lockhart Patent for teaching an array of probes (see *e.g.*, Answer at page 12, second paragraph). However, combining this teaching of the Lockhart Patent with Lo produces an inoperable method, since Lo uses an array (a positionally-addressable matrix) of samples, as discussed above under the heading "Claims 61-63 and 84." It is not at all apparent to Appellant how one could hybridize an array of probes as in the Lockhart Patent (situated in different locations on a solid support) to an array of test dots (situated in different locations on a solid support). Instead, it seems impossible. Where a proposed modification would render the prior art inoperable for its intended purpose, there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900 (Fed. Cir. 1984).

Accordingly, the Examiner's response to Appellant's argument C1 is erroneous, and the rejection of claims 66 and 74 should be reversed.

The Examiner's Response to Appellant's Argument C2 Related to Claim 75 Is Erroneous

With respect to Appellant's argument C2 relating to claim 75, the Examiner contends that:

> [T]he Lockhart Patent clearly teaches the advantages of hybridization wherein the sample comprises multiple different polynucleotides whereby differentially labeled nucleotides can be analyzed independently. Therefore, it would have been further obvious to differentially label the different polynucleotides of Lo et al to thereby provide for independent analysis of simultaneously hybridized polynucleotides as taught by the Lockhart Patent (Column 24, lines 59-67).

(Answer at page 19, third paragraph, bridging to page 20, first paragraph). Appellant respectfully disagrees.

Appellant respectfully submits that the Examiner's above-quoted contention relating to differential labeling is irrelevant to the additional limitation recited in claim 75 of the instant application and argued by Appellant for separate patentability. Claim 75 recites the additional limitation that the first sample comprises two or more different polynucleotide molecules, wherein none of the two or more different polynucleotide molecules hybridizes or cross-hybridizes to a probe that also hybridizes or cross-hybridizes to another one of the two or more different polynucleotide molecules. Since Lo does not know the base sequence of any of its probes nor the sequences of nucleic acid molecules in its test dots (and since Lo does not present any such cross-hybridization data for molecules within a test dot), Lo cannot teach or suggest a method using such a sample. Both the Lockhart Article and the Lockhart Patent also do not disclose the first sample of claim 75. Thus, irrespective of whether the Lockhart Article or the Lockhart Patent teaches differential labeling with fluorescence labels or attaching probes to microarrays, they do not provide motivation to a person skilled in the art to modify the method of Lo in such a way as to render the presently claimed invention of claim 75 obvious.

Accordingly, the Examiner's response to Appellant's argument C2 relating to claim 75 is erroneous, and the rejection should be reversed.

The Examiner's Response to Appellant's Argument C3 Relating to Claim 85 Is Erroneous

With respect to Appellant's argument C3 relating to claim 85, the Examiner contends that:

> [T]he claims merely require that the second sample lack some (undefined) polynucleotides of the first sample. Hence, any nucleotide sequence (e.g. any two bases) in the first sample, not presence in the second sample. Because the first and second polynucleotide samples are different, as acknowledged by Appellant, the second sample lacks some polynucleotides as claimed

See Answer at page 20, second paragraph. Appellant respectfully disagrees.

Claim 85 recites "wherein the second sample lacks polynucleotide ***molecules*** of said first sample." As such, as in claim 85, all of the polynucleotide ***molecules*** of the first sample are precluded from the second sample. In contrast, Lo teaches that *N. gonorrhoeae* and *N. meningitidis* have high sequence homology. Thus, a person skilled in the art would expect that Lo's second sample, *i.e.*, test dots of *N. meningitidis*, ***might*** comprise polynucleotide molecules that are also contained in the first sample. In any event, Lo clearly does not teach or suggest that its test dots of *N. meningitidis* chromosomal DNA fragments do not contain any of the same molecules present in the test dots of *N. gonorrhoeae* chromosomal DNA fragments. The Examiner appears to be misinterpreting the claim as reciting that the second sample comprises polynucleotide molecules that lack a ***nucleotide sequence*** in the polynucleotide molecules of the first sample. This is not what the claim recites.

Accordingly, the Examiner's response to Appellant's argument C3 relating to claim 85 is erroneous, and the rejection should be reversed.

Thus, Appellant respectfully submits that Lo, the Lockhart Article, and the Lockhart Patent, do not render claims 61-63, 66, 74-75 and 84-85 obvious. The rejection is in error, and should be reversed.

III. CONCLUSION

For all of the reasons set forth above, Appellant respectfully requests that all of the rejections of the claims on appeal be reversed.

Respectfully submitted,

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